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RESULTS OF RESEARCH ON ULCEROUS DISEASES IN HUNGARY

A Magyar Tudomany Tiz Eve
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Ulcerous diseases have been continuously increasing in modern times. The cause of ulcerous diseases is not known. According to the present author ulcerous diseases are in the class of vegetative diseases, which includes diseases such as high blood pressure, calculus disease, asthma, etc. The origin of vegetative diseases is traced back to a disturbance of the coordinated functioning of a regulating system. This regulating system has 3 parts, influences from the external environment which effect man and the central nervous system which receives, and partly protects man from these influences, and finally, the diseased organ, which in the case of ulcerous disease is the stomach. An ulcerous disease, then, is not a local disease of the stomach, and this is what is intended to be expressed by the term ulcerous disease.

The present author estimates that 10% of the adult Hungarian population suffers from ulcerous disease.

Research on gastric diseases in Hungary has little traditional background. In contrast to the expansion of research on heart and liver ailments on the basis of the work of Sandor Koranyi, for example, very little has been done in the field of gastric diseases. Rezso Balint was the only outstanding Hungarian clinician to conduct research, with the cooperation of some of his students, on the clarification of the origin of ulcerous disease. Although his theory that the acidity of the fluids of the body have an important role in the origin and difficult therapy of ulcers was proved wrong, it is to his credit that he did arouse the interest of competent scientists such as Fornet and Rosenthal concerning the problem of ulcerous diseases.

At present, no regular research is being done by theoretical institutes on the origin of ulcers, with the exception of the institute of pathology headed by Sos and the institute of pathological anatomy headed by Balo, where the effects of deficient nutrition, and of cerebral changes, respectively, are being studied in relation to the origination of ulcerous diseases. Among the clinics, organized research on this problem is being conducted only at the Szeged Internal Medicine Clinic No 1. Individual researchers are doing praiseworthy work amid difficult circumstances in hospitals, SzTK out-patient clinics, etc. Outstanding among the latter are Laszlo Friedrich, Gyorgy Szemzo and Jozsef Vandorfy. On a practical scale, the determination of the value of individual therapeutic measures and publication of certain very interesting cases is done by the medical periodicals.

The investigations of the present author and his associates (Hamori, Scossa, Borbola, Bikich, Faredin, and Novaszel) are directed primarily at clarification of the circumstances attending the origin of ulcers. In the animal experiments of this group the so-called actophane ulcer of the dog was chosen as a model of the human ulcer (3 weeks of treatment with actophane produces an ulcer in the stomach of a dog which is very similar to human gastric ulcer). During the course of investigation of the role of the central nervous system it was found that an incision in the main nerve of the stomach, the vagus nerve resulted in the formation of especially severe ulcers. Leucotomia, which consists of cutting the

connection between the temporal cerebral cortex and the midbrain, and which has been customarily used in certain mental diseases, had similar drastic results. Experiments performed in conjunction with Imre Magyar as early as during World War II showed that prolonged narcotic sleep prevents, and prolonged prevention of sleep through artificial stimulation furthers the origination of ulcers. These results are in accordance with the findings of Pavlov and his associates, who observed the beneficial results of prolonged narcotic sleep in the treatment of ulcer patients.

The most important achievement of the clinic headed by the present author was the discovery that the release of very large quantities of histamine in the mucous membrane of the stomach has a significant role in the direct formation of ulcers. Histamine or its precursors are found in all cells of the body. However, it still has not been established whether histamine is important in the normal body, or whether it is released only under pathological conditions, when a cell is damaged. It was found that atophane-induced ulcers contain considerable amounts of histamine and that increased amounts of histamine are found in the region toward which the ulcer is growing. This fact later was observed in human gastric ulcers, also. This was possible through the examination of human stomachs in gastric ulcer cases requiring surgery, which were placed at the disposal of the research group by the operating surgeon. Artificial damage of the gastric mucous membrane is not accompanied by an increase in the local release of histamine, nor was there an increase in histamine at the site of ulcerous gastric cancers. Therefore, according to the above, an increase in liberation of histamine is a specific phenomenon for both atophane-induced ulcer and human gastric ulcer.

How may this increase in the release of histamine be explained? Active and inactive phases may be distinguished in the course of an ulcerous disease. In the inactive phase the presence of an ulcer cannot be demonstrated, the patient is free from symptoms and has a healthy, varied appetite. In the active phase the ulcer appears and spreads, and may be accompanied by various complications. The author and his associates examined the histamine content of the gastric juices of the same patient in the active and inactive phases. It was found that the histamine content of the gastric juices during the active phase was considerably decreased or nonexistant, and in the inactive phase the histamine content returned to normal or was even hypernormal. In the light of the above this fact may be explained by the existence of a presently unknown mechanism which effects removal of superfluous amounts of histamine collected in the stomach wall, thereby preventing damage in this area by the histamine. It is proposed that this mechanism does not function in the active phase of ulcerous disease. The result of the latter is that histamine collects in the stomach wall (and leads to the formation of an ulcer), and is prevented from reaching the stomach cavity, or is released into the lumen in very small amounts. The change to the inactive phase coincides with the reactivation of the histamine-removing mechanism, which begins carrying off the accumulated histamine. At present it is not known which factors regulate this peripheral system which regulates the histamine balance of the stomach. The working hypothesis of the research group is that the principal regulating factor is the central nervous system and the glands of internal secretion (the adrenal glands?) which it controls.

The investigations of Balc and his associates on ulcers which arise following cerebral hemorrhage indicate that the central nervous system has an important role in the origin of ulcers. Along the same line Freisinger and Bikali tied off the two vagus nerve trunks of rabbits with sutures soaked in carboxylol. Hemisection of the vagus nerve trunks results in considerable loss of tonus of the stomach wall, and if this is aggravated with papaverine very severe ulcers are formed.

Biro and Nagy investigated the relationship between ulcerous diseases and the functioning of the adrenal glands. These researchers found a weakening of the activity of the adrenal cortex during the active phases of ulcerous disease, and some therapeutic success was achieved through the use of adrenal-cortex-supplementing measures. Clinical studies which have shown that the production of 17-ketosteroids (which are mostly the products of decomposition of the adrenal cortical hormones) decreases considerably during the active phase of ulcerous disease also may be of importance in determination of the role of the adrenal cortex. Using the Thorn test, Foti also found deficient functioning of the adrenal cortex in the active phase of ulcerous disease.

Sztanojevits, Monus and Korpassy succeeded in inducing acute ulcers in rats through the feeding of tannic acid. Filipp is of the opinion that allergies (hypersensitivity) are important in the origination of ulcers, and succeeded in inducing ulcers in cats through the repeated induction of anaphylactic shock accompanied by damage to the gastric mucous membrane through the introduction of alcohol.

Friedrich attributes the origination of ulcerous disease to the fact that the gastric juices of ulcerous patients lacks some substance which is present in gastric juices of a healthy individual, and this lack makes the origination of ulcers possible. He supports this viewpoint with experiments on animals.

It is a debatable question whether gastric and duodenal ulcers are the same disease. The present author also had advanced many arguments to the effect that these two are not identical, but are similar diseases.

A review of the data of any therapeutical institution on ulcerous diseases gives a good picture of the variations in the frequency of incidence and in the clinical course of this disease. Such reports were prepared by the Pecs (Benko and Marth), Debrecen (Ban) and Szeged (Hetenyi) internal medicine clinics and by Szemzo, who developed the enormous Budapest SzTK data (approximately 26,000 cases, including 1,690 ulcers).

It is not always easy to determine whether the ulcer of an ulcer patient is in the active or passive phase. This problem is very important to the determination of the work capacity of the patient. Pain is a definite indication of ulcer activity, but its control is difficult. X-ray examinations are not always conclusive because the period of healing of the ulcer may extend far into the inactive phase. Erdelyi emphasizes the importance of those x-ray observations which may be attributed the nervous irritation of the area surrounding an ulcer. Two new methods were developed at the author's clinic for the determination of the active phase of ulcerous disease: (1) determination of the histamine content of the gastric juices, and (2) determination of the 17-ketosteroid content of the urine. Both these values decrease during the active phase. However, both these tests are complicated, require specially-equipped laboratories, and are not suitable for series examinations. Therefore, other methods are being sought, but at present no simple, reliable method has been found. Friedrich and Tibor also obtained similar results. Navaszel, Faredin, Varro and Farage contend that increased acid and pepsin secretion is an indication of the active phase of duodenal ulcer.

Many researchers have been occupied in furthering the diagnosis of ulcerous disease. A lengthy discussion of x-ray diagnosis by Erdelyi has appeared in print. Rethelyi has published an account of x-ray examination of ulcer of the fundus of the stomach which, although

relatively rare, is important because of the possible confusion with cancer. Friedrich and Szemzo both have reported on the mirror examination (gastroscopic) method. Friedrich has described a new symptom of ulcerous disease (the gyrus symptom). Otvos has evaluated the results of the atropine test which he had developed.

Complication of ulcerous disease makes this disease a serious illness. In this sense it is understandable that part of the appurtenant literature, contributed chiefly by hospital wards, has been concerned with this problem. Feszler takes a radical viewpoint: he would have all hemorrhaging ulcer patients relegated to surgical wards. If the hemorrhage does not cease within a short time he recommends surgery with local anesthesia, with excision of 2/3 of the stomach. However, he recommends surgery even if the hemorrhage stops and the patient recovers from the effects of the hemorrhage. In opposition to this standpoint the present author has recommended internal medicine therapy first, in the case of hemorrhaging ulcer, and contends that surgery is necessary in only a small percentage of the cases. The latter would include cases in which hemorrhage did not stop after internal medicine therapy, patients over 50 years of age, and cases of repeated hemorrhaging.

Many reports have been published on the course of treatment following perforation of the ulcer. It previously had been considered an error to fail to undertake surgery immediately. However, since Taylor, in England, reported that the internal medicine treatment of perforated ulcer has no worse results than surgical treatment, an intense literary battle has begun concerning this problem, in which Hungarian doctors also have participated. The general opinion is that surgery is still the major form of treatment and that conservative treatment is recommended only in cases in which the diagnosis is not definite or in which the patient cannot be transferred to a surgical ward (Cukor, Szepes, Litman-Mathe, and Friedrich). It is also debated whether in cases of perforated ulcer the surgeon should merely suture up the ulcer, or whether the ulcer, and 2/3 of the stomach should be removed (Kormendy-Ekes, Szappanos). Ladanyi and Haraszti reported as a medical curiosity, a case in which a gastric ulcer broke through the left heart ventricle. The patient died under surgery. Litman and Jellinek described a case in which an abcess resulting from perforation of the stomach wall continued for 2-1/2 years with no serious symptoms.

A research group consisting of Korpassy, Ormos, Bachrach and Bence is investigating the problem of the transition of gastric ulcer into gastric cancer (the so-called ulcus-carcinoma). This condition was found in 5.9% of all the ulcer cases at the Institute of Pathological Anatomy of the Szeged University. In the opinion of these researchers the tendency toward cancer formation is found particularly in the ulcers of elderly male patients or in the case of very large ulcers. They state that the formation of cancer from an ulcer may be determined only by careful and circumspect pathological histological examination. These are the very difficulties which prompted the present author to assume a doubtful attitude toward the question of the transformation of ulcers into cancer. Szemzo describes the use of the gastroscope in several cases.

The course of ulcerous disease cannot be predicted. The inactive phase may extend into a period of years, and often it cannot be definitely ascertained what caused the change-over into the active phase. Such apparently spontaneous fluctuations make the evaluation of individual therapeutic measures extremely difficult. The patients symptoms subside even in the active phase if the patient is simply

confined to bed and is fed frequently. All that the present therapeutic measures can achieve is the transition of the patient from the painful phase into the inactive phase so that the ulcer can heal. No available method can guarantee a life-long cure from ulcer. Approximately 25% of ulcer patients are permanently cured, and the remainder experience "recurrences" sooner or later, and new ulcers are formed, despite the therapeutic method used.

Under these conditions it is not surprising that Friedrich and Tibor, and Novaszel at the clinic headed by the present author, found that symptoms of more than half of the ulcer patients could be made to disappear through the administration of a placebo. In these cases the symptoms spontaneously subsided.

Kopasz, and a team consisting of Nagy, Gergely, and Varnai described the use of the Pavlovian extended narcoticsleep therapeutic method. Although the immediate results of this method are good, the long-range results are no better than those obtained by other methods, which is in keeping with the observations of the present author. Proceeding from the point of view that due to tissue congestion the blood vessels at the base of the ulcer are collapsed, Vandorft proposes the use of a drug (dicumarin) which will relieve this congestion. On the basis of his "lacking principle" theory described above, Friedrich is having gastric ulcer patients swallow gastric juices taken from patients whose gastric ulcers have healed. Friedrich and Takacs, and Vargha have experimented with the administration of liquorice (liquiritia) extract suggested by a Dutch doctor, and have reported good results with gastric ulcer patients. Unfortunately extended administration of this extract results in the production of harmful side effects. Friedrich and Foti recommend x-ray radiation of the sympathetic border trunk.

In the field of surgical treatment of ulcerous disease, Lazar analyzed the total surgical data of the Budapest Surgical Clinic No 1 and found that, corresponding to the general experience in this field, the operation most frequently used at present, resection of 2/3 of the stomach, resulted in complete cure in 90% of the total number of cases. Jaki has published a summary of the present status of the problem of the indication of surgical necessity.

The recommendation that ulcer be treated through hemisection of the vagus nerve aroused great international interest. However, as is usual in such cases, this surgical method was enthusiastically applied at first, but later as the disadvantages of this operation became evident it was used less frequently, and at present is recommended only in certain limited cases. In Hungary, Hedri, Szemzo and Zsebok described their extensive experiences in this field.

Whereas ulcerous disease usually is a life-long affliction, the patient should be under the observation of a doctor even in the inactive intervals. This principle has been pursued in heart, tuberculosis, and in some instances, diabetic patients, with the establishment of a system of medical supervisors and the construction of consultation institutes. Attempts currently are being made to ensure the supervision of high blood pressure patients. Attempts at such care for ulcer patients has been undertaken only on a local scale, and that only in recent years. The Internal Medicine Specialist Group has discussed this problem twice (in 1950 and in 1953), and 3 special meetings have been held at Szentes for the discussion of this problem.

The problem of rehabilitation shows even less favorable results. Rehabilitation is taken to mean the relocation of certain ulcer patients

in a different occupational field when it is deemed necessary by a doctor. The solution of this problem also requires organized, central administrative action.

The great increase in the number of ulcerous patients has made the control of this disease a public health task of primary importance. Therefore, by way of conclusion, the following tasks which await solution by the public health administration are listed: (1) increased support of research on ulcerous disease, (2) the designation of several hospital wards as ulcerous disease wards (or gastroenterological wards) for the work of ulcerous disease research, and (3) national organization of ulcerous disease treatment and rehabilitation. All personnel and material resources are available for a considerable increase in research on gastric and intestinal diseases and the expert treatment of patients suffering from diseases of these organs in Hungary.

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